HOSPITAL CHRONICLES 2008, SUPPLEMENT: 46–51

ATHENS CARDIOLOGY UPDATE 2008

Assisted Circulation for the Failing Heart: Experience with the Novacor Left Ventricular Assist System

Emily A. Farkas, MD, John A. Elefteriades, MD

Yale University School of Medicine; Department of Surgery, Section of Cardiothoracic Surgery, New Haven, CT, USA

KEY WORDS: *advanced heart failure; assisted circulation; mechanical circulatory support; Novacor; surgical therapy for heart failure; ventricular assist device*

ABSTRACT

Surgical therapy for the treatment of heart failure is a relatively young solution to a problem that has overwhelmed civilizations dating back to the First Dynasty. Despite centuries of enormous multi-disciplinary medical and technological advance, in 2006 nearly two thousand Americans died of cardiovascular disease each day, averaging 1 death every 35 seconds, and claiming more lives than the next 4 leading causes of death combined [1]. In 2007, one in 30 female deaths will be from breast cancer, while 1 in 2.6 will be from cardiovascular disease [2]. The prevalence of heart failure in our population is a staggering 5 million in the United States, and 6.5 million in Europe. Furthermore, based on the 44 year follow-up of the National Heart, Blood, and Lungs Institute Framingham Heart Study, 80% of men and 70% of women under age 65 who have heart failure will die within 8 years [3]. The focus of this article will be to review the history and future of the Novacor Left Ventricular Assist System (LVAS) as it relates to the failing heart; the story of how the innovator, the researcher, the engineer, and the surgeon have come together to offer a surgical solution to a medical problem of inconceivable scope.

INTRODUCTION: THE HISTORY OF HEART FAILURE

Circa 1500 B.C. on the West Bank of the Nile in the necropolis of ancient Thebes, the Ebers Papyrus documents Egyptian priest-physicians using the sea onion or squill to treat excess blood in the heart and lungs [3]. Medicinal plants for the treatment of 'dropsy' were favored by Hippocrates, the subject of a treatise by Pythagorus, and the foundation of our current medical therapy as highlighted by the utilization of digitalis from the foxglove flower in the late 1700s [4]. With the advent of cardiopulmonary bypass two centuries later, the transition to potential surgical alternatives was fully realized with the first orthotopic heart transplantation by Barnard in 1967 [5]. Yet as medical therapy is limited by the progression of disease, and as organ replacement is limited by the shortage of donation, assisted circulation has emerged as one of the most promising treatments of the failing heart in our era. The evolution continues, beginning as a temporizing Bridge-to-Transplantation, and developing into Destination Therapy, an apt name in a journey to treat an ailment that was first encountered several hundred years before the birth of Christ.

Address for correspondence:
john.elefteriades@yale.edu

BODY OF REVIEW

A variety of technologies have been designed to mechanically assist circulation. All of these systems provide energy for the forward flow of blood in the body to relieve the left heart of this charge, while allowing differing degrees of pressure and volume unloading of the ventricle. The devices as well as their power sources may be implanted internally or placed in a paracorporeal position. Both electric and pneumatic driven mechanisms are available, and flow characteristics can be categorized as pulsatile or non-pulsatile in nature. Devices may be utilized as a temporizing measure for Bridge-to-Transplant (BTT) therapy while awaiting organ availability, while some may be implanted as an alternative to transplantation, which is designated as Destination Therapy (DT) for those patients with poor candidacy for organ replacement.

The Novacor® Left Ventricular Assist System (WorldHeart Inc., Oakland, California) has emerged as one of the most reliable devices in this competitive market. Scientists in Berkeley, CA began developing the system in 1969 based on a pulsed-solenoid driver concept, and 15 years later the world's first human implant and successful Bridge-to-Transplant operation was successfully performed with the Novacor LVAS. In 1994, the device received regulatory approval for European Commercialization (CE Mark) without restriction as to the indication for use, and in 1998, Food and Drug Administration (FDA) approval for U.S. sales as a Bridge-to-Transplant system was acquired.

The WorldHeart Novacor LVAS is an electro-magnetically driven device that has an implantable pump and paracorporeal power source that provides pulsatile flow for circulatory support (Fig. 1). Blood enters the device through an inflow conduit connected to the recipient's left ventricle. Circulation is supported as the pump ejects blood in parallel through its own outflow conduit into the arterial system, most commonly the distal portion of the ascending aorta. The system is completely self-regulating, automatically adjusting its beat rate and stroke volume in response to the recipient's changing hemodynamic requirements.

The power source is an external Controller that regulates pumping action and monitors system function, alarming for out-of-range operation or fault conditions (Fig. 2). A small tube, often referred to as the drive line, contains control and power wires and traverses the patient's skin to connect the implanted pump to the external Controller. Two rechargeable batteries provide power to the Controller (Fig. 3), and these portable power packs may be worn on a belt or carried in a vest, shoulder bag, or backpack. The nickel-metal hydride power packs have been recently enhanced to last approximately 8 hours per pair at an output of 6 L/min. A personal monitor, designed for in-home use, supplies power to the Novacor when the recipient is sleeping, and also evaluates device function,

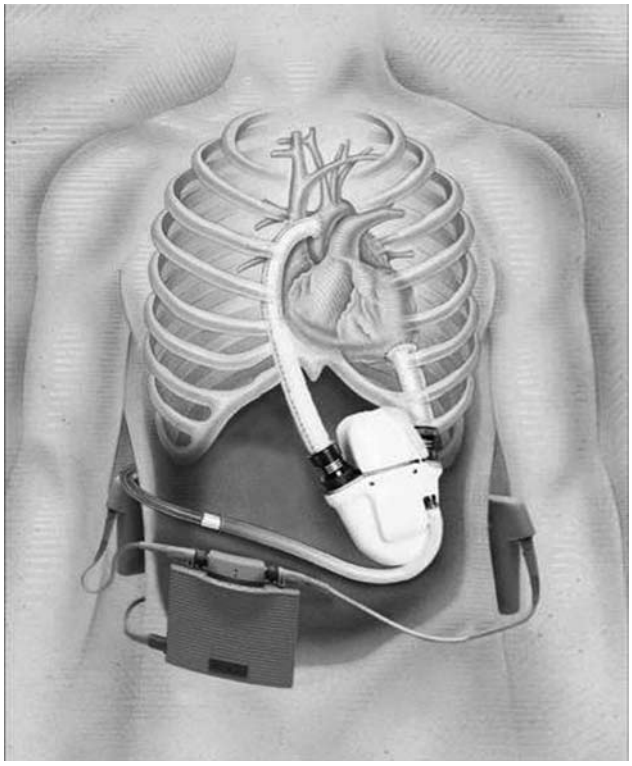

FIGURE 1. The Novacor LVAS I implantable system. Blood enters the device through the inflow conduit from the left ventricle, and pumps blood to the body through the outflow conduit to the ascending aorta.

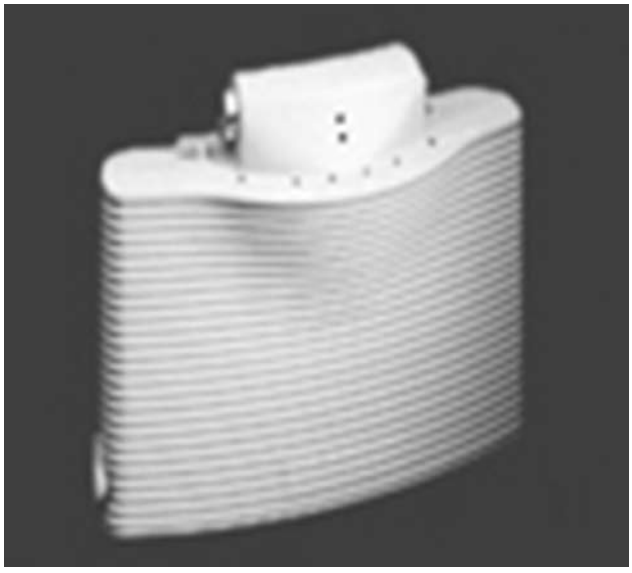

FIGURE 2. The external Controller regulates pumping action and monitors system function.

FIGURE 3. Rechargeable nickel-metal hydride (Ni-MH) battery lasts approximately six hours per pair (at an output of 6L/min).

providing an alarm and instructions in the event of a detected fault. A standby power source provides power to the monitor in case of an AC power outage.

Implantation is performed with the assistance of cardiopulmonary bypass through a median sternotomy incision extended halfway to the umbilicus. Most commonly, a pocket for the pump is developed posterior to the left rectus abdominus muscle and anterior to the left posterior rectus sheath from the costal margin to the iliac crest. The inflow conduit is tunneled from the pump pocket to the apex of the heart in the pericardial cavity and implanted in the left ventricle. The outflow conduit courses along the right pleural space to connect the pump to the ascending aorta. Finally, the drive line is tunneled through the subcutaneous tissue to exit the skin in the right lower quadrant of the abdomen, connecting the pump to the external controller. The patient is then weaned off of cardiopulmonary bypass and onto Novacor left ventricular assistance.

Left heart hemodynamic indices are uniformly improved with the institution of Novacor circulatory support, as evidenced by statistically significant increases in cardiac output and decreased pulmonary capillary wedge pressures, usually within 24 hours of implantation [6-9,12]. Functional right heart recovery is not as consistently realized, but most trials demonstrate a trend toward significantly improved right ventricular ejection fraction and decreased central venous pressure and pulmonary vascular resistance with the Novacor system [6,7,9,10]. In patients receiving LVAS assistance for more than 20 days, improved end organ function has been documented with improved hepatic and renal function prior to transplantation [6,10].

Early in the Novacor experience, thromboembolism was a major concern during mechanical circulatory support. Larger studies have documented the rate of embolic cerebrovascular accident (CVA) as high as 29.0% in previous years [11-13]. A recent review of the collective experience among the 8 most active centers in North America and Europe demonstrates that the current rate of embolic stroke has been reliably reduced to 5.3% (Fig. 4) [14]. While modification of anticoagulation protocols has been instituted, the most likely explanation for this approximately 85% decrease in the rate of cerebrovascular events is the revision of the Novacor inflow conduit with a material that is less thrombogenic [9,12]. Other complications such as infection have also become less frequent with subtle changes in operative techniques such as immobilization of the driveline at the skin exit site, meticulous tailoring of the pump pocket, and aggressive drainage of potential sites of fluid collection in the early peri-operative period [9,12,15]. In striking contrast to other systems, only 1.4% of Novacor devices have required replacement over their lifespan, indicating an unparalleled degree of reliability (10).

Much of the earlier literature addressing survival outcomes focused on comparisons between the two major pulsatile pumps, the Novacor LVAS and the Thoratec HeartMate Implantable Vented Electric System (Thoratec Corportation, Pleasanton, CA). A prospectively designed trial at a single center enrolled 40 patients and found that survival to transplantation was 65% for the Novacor group and 60% for the HeartMate recipients [16]. A more recent study has reproduced this trend with a 69% survival to transplant with patients receiving the Novacor device, and a 61% survival in recipients of the HeartMate system. Kaplan-Meyer 5-month survival post-LVAD was 89% for the Novacor group and 83% for the HeartMate group [11]. There have been over 1700 successful

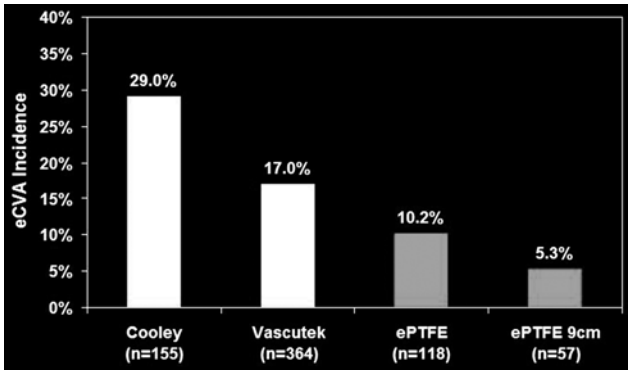

FIGURE 4. Incidence of embolic cerebrovascular accidents (eCVA) with different types of inflow conduits.

Novacor implantations worldwide with multiple reports of continued use for over four years without device malfunction [9,17]. In July 2006, a patient in Tennessee entered his sixth year of continuous support with his original Novacor LVAS (10). At the time of publication, this is the longest documented period of circulatory assistance without the need for device exchange among all pulsatile systems worldwide.

CONCLUSION

For patients awaiting transplantation, the Novacor LVAS has demonstrated consistently favorable outcomes and unmatched durability. Two landmark investigations have not only confirmed this performance, but have also proven the superiority of Novacor mechanical support to medical therapy, as well as set the stage for its next logical application in Destination Therapy. The REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure), a multi-center study supported by the National Heart, Lung, and Blood Institute , compared long-term implantation of left ventricular assist devices with optimal medical management for patients with end-stage heart failure who require, but do not qualify to receive, cardiac transplantation. One hundred twenty- nine patients were randomly assigned to either LVAD support or optimal medical management. Survivals at 1 year were 52% in the device group and 25% in the medical therapy group ($p = .002$) and at 2 years 23% and 8%, respectively ($p = .09$) [18]. Similarly, an FDA approved, prospective, multi-center, non-randomized controlled trial called INTrEPID (Investigation in Non – Transplant Eligible Patients who are Inotrope Dependent) demonstrated that patients receiving a Novacor LVAS had an average survival time more than three times longer than control patients who received optimal medical therapy but no device. In addition, patients receiving mechanical support scored significantly higher on standard measures of quality of life than patients in the control group (10).

EXPERT COMMENTARY

As one of the most active centers in North America utilizing the Novacor LVAS, our institution has found the reliability of the Novacor system to be a critical and attractive feature. Additionally, we have witnessed the dramatic decline in cerebrovascular events at our own and other centers world-wide following the inflow conduit refinements, briefly described earlier in this review. The initial Cooley® conduit that was utilized from 1984 to 1998 was fabricated from woven low-porosity polyester that contributed to sub-optimal mural flow and was prone to radial pulsation from its unsupported structural design. This combination resulted in the formation of a poorly attached, friable pannus within the graft and consequent propagation of particulate emboli (Fig. 5).

Redesigned in 1998, a Vascutek® (Terumo Company, Scotland, UK) inflow conduit was developed from knitted gel-sealed uncrimped polyester, yet still suffered from the formation of a thin, adherent pannus (Fig. 6). Two years later an expanded polytetrafluoroethylene (ePTFE) inflow conduit was introduced based on its 25-year history as a proven biocompatibible material in vascular applications, with particular suitability in the setting of venous flow dynamics (Fig. 7). Features include an integrally supported construction with an uninterrupted luminal surface not penetrated by sutures, and an outer impermeable coating that blocks transmural

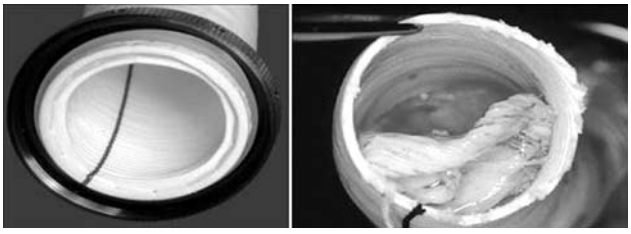

FIGURE 5. A) The Cooley inflow conduit was fabricated from low-porosity polyester that resulted in B) a poorly attached, friable pannus.

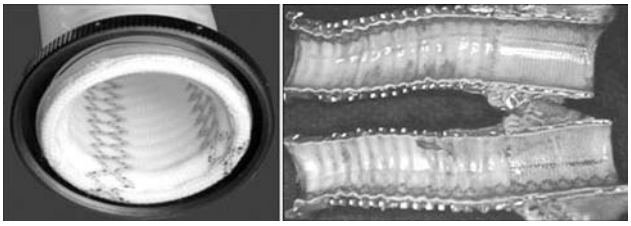

FIGURE 6. A) The Vascutek conduit was developed from knitted gel-sealed polyester, yet still suffered from the formation of B) a thin, adherent pannus.

FIGURE 7. A) The expanded PTFE conduit was developed with a smooth surface resulting in a reduced inflammatory response and B) no pannus.

penetration by inflammatory mediators and prevents adhesion formation. The result is a refined inflow conduit that has markedly decreased the incidence of embolic CVAs in this patient population [12,13,17]. We prefer the 9-cm model due to optimal anti-thrombotic performance evaluated in multicenter experience (Fig. 8) [14].

Our intraoperative management of coagulation involves the utilization of an antifibrinolytic agent, a standard cardiopulmonary bypass dose of heparin, and subsequent full reversal guided by activated clotting time (ACT) surveillance. In the early post-operative period, when chest tube drainage has decreased to less than 60 milliliters/hour for 3 consecutive hours, we initiate heparin therapy accompanied by aspirin and clopidogrel. Transition to coumadin usually occurs over 3 to 7 days when platelet function has stabilized and hepatic function has returned to near-normal conditions.

Our application of these protocols in combination with appropriate candidate selection and thoughtful surgical planning has allowed our patients to benefit from the unmatched durability of the Novacor LVAS. Recalling its success as the first system to surpass six years of support in a single patient, and the designation as the first and only device to meet the multi-year Device Readiness Test Protocol of the U.S. National Institutes of Health, we anticipate similar promise from, and expanded utilization of, future generations of WorldHeart devices.

FIVE-YEAR VIEW

Patients with end stage heart disease have many compelling reasons to consider surgical treatment in the current era. The next five years, however, will witness a revolution in both the way that mechanical support is provided, and in the population to which it is applied.

Technologists will focus on the development of new devices with smaller sizes, improved longevity, and the transcutaneous transfer of energy. WorldHeart is strategically positioned for the future with two new devices awaiting the completion of clinical trials. The Novacor LVAS II is the next generation pulsatile device that is smaller than its predecessor, fully implantable, and magnetically driven to eliminate wearing elements. This device entered the phase of animal testing in 2005. Similar enthusiasm also surrounds the WorldHeart Levacor Rotary VAD, which is an advanced, fourth-generation continuous flow pump that uses magnetic levitation to fully suspend the spinning impeller inside a compact housing. Encouraging results followed its first clinical use in Europe, and have been highlighted by feasibility trials initiated in Canada earlier this year (10).

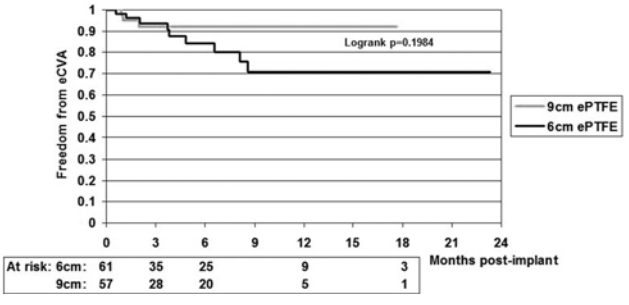

FIGURE 8. Comparison of freedom from embolic stroke with 9cm and 6cm ePTFE inflow conduits.

Clinicians will be challenged with perhaps the greatest responsibility for the continued development of surgical therapy in heart failure. Commitment to multi-disciplinary education and collaborative therapeutic planning amongst different specialists will identify patients who can benefit from elective rather than urgent mechanical support. Dedicated centers will also be able to offer individualized care; although it was felt by many that the Novacor was 'un-weanable', in 2005 our institution was the first in the United States to successfully wean a patient from her Novacor LVAS following a viral cardiomyopathy, biventricular failure, and cardiogenic shock.

In the future, the innovator, the researcher, the engineer, and the physician will continue to work in concert to provide assisted circulation to a variety of different patient populations in various clinical settings with a spectrum of personalized needs, and they will provide this amazing technology one failing heart at a time.

REFERENCES

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ,Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R,Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006 Feb 14;113(6):e85-151. Epub 2006 Jan 11. Erratum in: Circulation. 2006 Apr 11;113(14):e696. Circulation. 2006 Dec 5;114(23):e630.
2. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M,Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007 Feb 6;115(5):e69-171. Epub 2006 Dec 28.

3. Lloyd-Jones, D. M., Larson, M. G., Leip, E. P., Beiser, A., D'Agostino, R. B., Kannel, W. B., Murabito, J. M., Vasan, R. S., Benjamin, E. J., and Levy, D. Lifetime risk for developing congestive heart failure- The Framingham Heart Study. Circulation 106(24), 3068-3072. 12-10-2002
4. Podolsky, E. The search for heart remedies. Can Med Assoc J. 1934 September;31(3):310–315.
5. Barnard CN. Human cardiac transplantation. An evaluation of the first two operations performed at the Groote Schuur Hospital, Cape Town.Am J Cardiol. 1968 Oct;22(4):584-96.
6. Vetter HO, Kaulbach HG, Schmitz C, Forst A, Uberfuhr P, Kreuzer E, Pfeiffer M, Brenner P, Dewald O, Reichart B. Experience with the Novacor left ventricular assist system as a bridge to cardiac transplantation, including the new wearable system.J Thorac Cardiovasc Surg. 1995 Jan;109(1):74-80.
7. Di Bella I, Pagani F, Banfi C, Ardemagni E, Capo A, Klersy C, Vigano M. Results with the Novacor assist system and evaluation of long-term assistance. Eur J Cardiothorac Surg. 2000 Jul;18(1):112-6.
8. McCarthy PM, Portner PM, Tobler HG, Starnes VA, Ramasamy N, Oyer PE. Clinical experience with the Novacor ventricular assist system. Bridge to transplantation and the transition to permanent application. J Thorac Cardiovasc Surg. 1991 Oct;102(4):578-86; discussion 586-7.
9. Faggian G, Santini F, Franchi G, Portner PM, Mazzucco A. Insights from continued use of a Novacor Left Ventricular Assist System for a period of 6 years. J Heart Lung Transplant. 2005 Sep;24(9):1444.
10. Kormos RL, Gasior T, Antaki J, Armitage JM, Miyamoto Y, Borovetz HS, Hardesty RL, Griffith BP. Evaluation of right ventricular function during clinical left ventricular assistance. ASAIO Trans. 1989 Jul-Sep;35(3):547-50.
11. Kalya AV, Tector AJ, Crouch JD, Downey FX, McDonald ML, Anderson AJ, Bartoszewski CJ, Hosenpud JD. Comparison of Novacor and HeartMate vented electric left ventricular assist devices in a single institution.J Heart Lung Transplant. 2005 Nov;24(11):1973-5.
12. Strauch JT, Spielvogel D, Haldenwang PL, Correa RK, deAsla RA, Seissler PE, Baran DA, Gass AL, Lansman SL. Recent improvements in outcome with the Novacor left ventricular assist device. J Heart Lung Transplant. 2003 Jun;22(6):674-80.
13. Mussivand T, Hetzer R, Vitali E, Meyns B, Noirhomme P, Koerfer R, El-Banayosy A, Wolner E, Wieselthaler G, Reichart B, Uberfuhr P, Halfmann R, Portner P. Clinical results with an ePTFE inflow conduit for mechanical circulatory support.J Heart Lung Transplant. 2004 Dec;23(12):1366-70.
14. Elefteriades JA, El-Banayosy A, Noirbomme P, Vitali E, Reichart B, Lansman SI, Hendry P, Kasirajan V. Reduced embolic complications with Novacor LVAS: A multicenter experience. J Heart Lung Transplant. 2005 24(26): 887.
15. Holman WL, Rayburn BK, McGiffin DC, Foley BA, Benza RL, Bourge RC, Pinderski LJ, Kirklin JK. Infection in ventricular assist devices: prevention and treatment.Ann Thorac Surg. 2003 Jun;75(6 Suppl):S48-57.
16. El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Minami K, Inoue K, Korfer R. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. J Thorac Cardiovasc Surg. 2000 Mar;119(3):581-7.
17. Potapov EV, Weng Y, Drews T, Jurmann M, Hetzer R. Longest time of support by the Novacor left ventricular assist device without pump exchange. Ann Thorac Surg. 2005 Dec;80(6):2421.
18. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med. 2001 Nov 15;345(20):1435-43. Summary for patients in: J Card Fail. 2002 Apr;8(2):59-60. J Card Fail. 2002 Apr;8(2):61-2.
19. www.worldheart.com (WorldHeart Inc., Oakland, California).